**Formulary Review**
**Synthetic Conjugated Estrogens, A**
**Executive Summary**

| | |
|---|---|
| **Generic Name:** | Synthetic Conjugated Estrogens A |
| **Proprietary Name:** | Cenestin™ (Duramed Pharmaceuticals, Inc) |
| **Dosage Forms:** | 0.625-mg and 0.9-mg film coated tablets formulated to slowly release the product over several hours<br>A 1.25 mg tablet has been submitted for approval to the FDA |
| **Indications:** | Treatment of moderate to severe vasomotor symptoms associated with the menopause |
| **FDA Review Status:** | 3S |
| **AWP:** | $52.04/100 – 0.625-mg tablets<br>$62.77/100 – 0.9-mg tablets |

**Clinical Pharmacology:** Postmenopausal estrogen use relieves symptoms of estrogen depletion (eg, vasomotor symptoms, atrophic vaginitis) and reduces the risk of severe coronary heart disease. Estrogens also reduce the rate of bone loss in postmenopausal women and reduce bone fractures.

**Similar Drugs:** See Table 1.

**Summary:** The safety and efficacy of synthetic conjugated estrogens, A were established in one small short-term clinical trial. The estrogen significantly reduced mean moderate-to-severe vasomotor symptoms at 4-, 8-, and 12-weeks. At week 12, the reduction with the active product was 81% vs baseline compared with a 58% reduction with placebo ($p < 0.010$). Adverse effects are similar to those seen with other estrogens. The recommended usual dose is 1.25 mg daily.

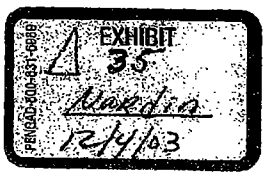


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Table 1. Comparison of esterified estrogens and conjugated estrogens[1-3]

| Parameter | Conjugated Equine Estrogens | Conjugated Estrogens, A | Esterified Estrogens |
|---|---|---|---|
| Labeled Indications | a. moderate-severe vasomotor symptoms of menopause<br>b. atrophic vaginitis<br>c. hypoestrogenism<br>d. breast cancer (palliation)<br>e. advanced androgen-dependent carcinoma of prostate (palliation)<br>f. osteoporosis | a. moderate to severe vasomotor symptoms of menopause | a. moderate-severe vasomotor symptoms of menopause<br>b. vulval and vaginal atrophy<br>c. hypoestrogenism<br>d. breast cancer (palliation)<br>e. advanced androgen-dependent carcinoma of prostate (palliation)<br>f. osteoporosis |
| Source | Not Synthetic<br>Extracted from pregnant mare urine | Synthetic<br>Derived from plant sterol precursors | Synthetic<br>Derived from plant sterol precursors |
| Contents of estrogenic substances | Estrone, equilin, 17α-dihydroequilin, and smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters | Sodium estrone sulfate, sodium equilin sulfate, sodium 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihyroequilin sulfate, sodium 17α-dihydroequilenin sulfate, sodium 17β-dihydroequilenin sulfate, sodium equilenin sulfate, sodium 17β-estradiol sulfate | Sodium estrone sulfate (75% - 85%), sodium equilin sulfate (6% - 15%) |
| Available tablet strengths | 0.3, 0.625, 0.9, 1.25, 2.5 mg | 0.625, 0.9 mg ** | 0.3 mg, 0.625 mg, 2.5 mg* |
| Usual dose for vasomotor symptoms | 1.25 mg daily | 1.25 mg daily | 1.25 mg daily |
| AWP† per 1.25 mg dose | $0.71 (Wyeth) | $1.04 (Duramed)‡ | $0.97 (Solvay brand)<br>$0.63 (Cheshire brand) |

*1.25 mg tablets available from Cheshire, per Drug Topics Red Book; ** 1.25 mg tablet pending approval; †from Drug Topics Red Book, 1999; ‡based on use of 2 0.625 mg tablets/dose. Cost is expected to decrease when 1.25 mg tablet is approved.

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**Synthetic Conjugated Estrogens, A**
**Monograph**

## Indications

Synthetic conjugated estrogens, A is indicated in the treatment of moderate to severe vasomotor symptoms associated with the menopause.[3]

The manufacturer has initiated clinical trials in the treatment of osteoporosis and for use in combination with medroxyprogesterone. A 1.25 mg tablet has been submitted to the FDA for approval. [4]

## Brief History of FDA Position on Synthetic Conjugated Estrogens

In 1997, the FDA announced that it would not approve synthetic generic forms of conjugated estrogens because the generic drugs could not be shown to contain the same active ingredients as the innovator. Natural conjugated estrogens (ie, Premarin®, approved in 1942) is obtained from the urine of pregnant mares and contains a number of different estrogens. This product has not been adequately characterized in terms of how each of these components contributes to the drug's overall effectiveness. Many experts believe that sodium estrone sulfate and sodium equilin sulfate are the primary active ingredients in Premarin®. Since 1970, the only two active ingredients in Premarin® listed by the US Pharmacopeia (USP) are estrone sulfate and equilin sulfate. Delta 8,9 dehydroestrone sulfate (DHES) is listed as an impurity, however Wyeth-Ayerst claims that the absence of delta 8, 9 DHES makes synthetic products compositionally different from the innovator drug.[5] Premarin® has not been shown to be superior to other marketed products. The FDA has requested that Wyeth-Ayerst further characterize the components of Premarin® and has stated that the company has committed to do so, although there is no timeframe for completion or monitoring system set by the company or agency.



 

Cenestin™ (synthetic conjugated estrogens A) was originally formulated as a generic product of Premarin®. Because of the 1997 FDA position on approval of an abbreviated new drug application (ANDA) for conjugated estrogens, Duramed Pharmaceuticals filed a NDA on March 17, 1998 for Cenestin™. On March 24, 1999, the FDA stated that adequate information was provided to establish the safety and efficacy of Cenestin™ doses ranging from 0.625 mg to 1.25 mg.[6] Moreover, the FDA assigned the designation "conjugated estrogens, A." Subsequent approvals of synthetic conjugated estrogens will be distinguished by B. C. D. etc. No synthetic conjugated estrogen product will be labeled USP until a drug monograph for the entire class is adopted. Thus, Cenestin™ is not a generic form of Premarin®, will be listed separately from Premarin® in the Orange Book, and will not be listed with a TE code.[4]

A synthetic conjugated estrogen product containing six conjugated estrogens is currently available in Canada and is indicted for the long-term treatment of osteoporosis. In Canada, this product (C.E.S.) is considered interchangeable with Premarin®.[7]

**Clinical Pharmacology**

Estrogens are essential to the development and maintenance of the female reproductive system and secondary sex characteristics. Declining estrogen secretion during menopause is associated with signs and symptoms of hormone deficits in estrogen-dependent organs (female genital organs, breasts, hypothalamus, pituitary). Pituitary gonadotropin secretion rises, reflected by increased quantities of gonadotropin in blood and urine. The endometrium becomes atrophic, myometrial mass decreases, and the vaginal epithelium becomes thin. Postmenopausal estrogen use relieves symptoms of estrogen depletion (eg, vasomotor symptoms, atrophic vaginitis) and reduces the risk of severe coronary heart disease. Estrogens also reduce the rate of bone loss in postmenopausal women and reduce bone fractures.[8]

Conjugated estrogens, A contains nine estrogens derived from plant sources (soy bean and yam), all of which are also included in Premarin®.[4]



 

**Pharmacokinetics**

Synthetic conjugated estrogens are soluble in water and well absorbed from the GI tract. The product is released from the tablet slowly over several hours, leading to maximum plasma concentrations within 4 to 16 hours. The effect of food on absorption has not been studied.[3]

Estrogens are widely distributed in the body. Conjugated estrogens bind primarily to albumin, while unconjugated estrogens bind to albumin and sex-hormone binding globulin (SHBG). Conjugated estrogens are metabolized in the same way as endogenous estrogens. Biotransformation among the various forms of estrogens takes place primarily in the liver. Estradiol is reversibly converted to estrone and both can be converted to estriol, the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, conjugation in the liver, biliary secretion of conjugates into the GI tract, and hydrolysis in the gut followed by reabsorption. Estradiol, estrone, and estriol, along with their glucuronide and sulfate conjugates are excreted in the urine. The apparent terminal elimination half-life of conjugated estrone is 4 to 18.5 hours and of conjugated equilin 4 to 17 hours.[3]

**Efficacy**

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*Summary*

One short-term (12 week) clinical trial conducted in 120 women evaluated the efficacy of synthetic conjugated estrogens A. This trial was published in abstract form.[9] Conjugated estrogens A significantly reduced moderate-to-severe vasomotor symptoms vs. placebo at 4, 8, and 12 weeks. Most women required a dose of 1.25 mg daily. There are no comparative trials with other estrogens.

A randomized, double-blind, multicenter, placebo-controlled trial was conducted in 120 healthy perimenopausal or postmenopausal women (72 active; 48 placebo) aged 38 to 66 years (mean, 48 years) to evaluate the efficacy of conjugated estrogens A in the treatment of vasomotor symptoms of menopause.[9] Patients were randomized to treatment with placebo or

 

Cenestin™ 0.625 mg daily for 12 weeks. Dose titration based on response was permitted after 1 week of treatment. The dose was increased to double the initial dose (2 X 0.625-mg active drug or 2 doses of placebo) in patients with an inadequate response or decreased to one-half the initial dose (0.3 mg daily or placebo) in patients who could not tolerate the higher dose. The mean number of moderate to severe vasomotor symptoms (MSVS) per 24 hours was assessed based on a patient-maintained diary of the number and severity of hot flashes. A 2-week baseline period was compared with the 4th, 8th, and 12th weeks of treatment. Enrollment required at least 60 MSVS per week during baseline. The average baseline was 96.8 hot flashes per week in the active treatment group and 94.1 hot flashes per week in the placebo group. The FDA requires that treatment of vasomotor symptoms be limited to patients with moderate to severe symptoms, so the study population reflects this population and not the general population. By week 12, 10% of active treatment patients remained on a dose of 0.625 mg daily and 77% were on a 1.25 mg daily dose. There were statistically significant differences from baseline between active treatment and placebo at week 4 ($p < 0.022$), week 8 ($p < 0.010$), and week 12 ($p < 0.010$; Table 3). At week 12, the mean reduction in MSVS was 81% (baseline average, 96.8 hot flashes per week; week 12 average, 16.5) in the active treatment group vs. 58% (baseline average, 94.1 hot flashes, week 12 average, 37.8) in the placebo group. A similar response was noted regardless of race or body weight.[3,9,10]

Table 3. Mean % reduction from baseline in the number of moderate-to-severe vasomotor symptoms in patients treated with synthetic conjugated estrogens, A vs. placebo.[3]

| Time point | Mean % Change in No. of Moderate-to-Severe Vasomotor Symptoms per 24 Hours* | | P-value |
|---|---|---|---|
| | Conjugated Estrogens, A | Placebo | |
| Week 4 | -68.1 | -48.4 | 0.0224 |
| Week 8 | -78.3 | -54.3 | 0.0101 |
| Week 12 | -80.3 | -56.3 | 0.0102 |

* Data presented in the product information are somewhat different from that presented in the abstract.

**Adverse Reactions**

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The most common adverse events reported during a 12-week clinical trial were headache (68%) and insomnia (42%), however, both occurred in a similar percentage of placebo-treated patients (Table 3). Other side effects reported with estrogens include nausea and vomiting,

 

breast tenderness or enlargement, enlargement of fibroid tumors, fluid retention, and spotty darkening of the skin.[3] Since conjugated estrogens, A is approved only for the treatment of vasomotor symptoms associated with menopause and not for osteoporosis, the FDA did not require long-term safety data. [4] Studies to support an osteoporosis indication are ongoing.

Table 3. Number (%) of patients with adverse events with a >5% occurrence rate[3]

| **Body System/Adverse Event** | **Cenestin (n = 72)** | **Placebo (n = 48)** | **Total (n = 120)** |
|---|---|---|---|
| # Patients with adverse events | 68 (94) | 43 (90) | 111(93) |
| Body as a Whole | | | |
| Abdominal pain | 20 (28) | 11 (23) | 31 (26) |
| Asthenia | 24 (33) | 20 (42) | 44 (37) |
| Back pain | 10 (14) | 6 (13) | 16 (13) |
| Fever | 1 (1) | 3 (6) | 4 (3) |
| Headache | 49 (68) | 32 (67) | 81 (68) |
| Infection | 10 (14) | 5 (10) | 15 (13) |
| Pain | 8 (11) | 9 (19) | 17 (14) |
| Cardiovascular System | | | |
| Palpitation | 15 (21) | 13 (27) | 28 (23) |
| Digestive System | | | |
| Constipation | 4 (6) | 2 (4) | 6 (5) |
| Diarrhea | 4 (6) | 0 (0) | 4 (3) |
| Dyspepsia | 7 (10) | 3 (6) | 10 (8) |
| Flatulence | 21 (29) | 14 (29) | 35 (29) |
| Nausea | 13 (18) | 9 (19) | 22 (18) |
| Vomiting | 5 (7) | 1 (2) | 6 (5) |
| Metabolic and Nutritional | | | |
| Peripheral edema | 7 (10) | 6 (13) | 13 (11) |
| Musculoskeletal | | | |
| Arthralgia | 18 (25) | 13 (27) | 31 (26) |
| Myalgia | 20 (28) | 15 (31) | 35 (29) |
| Nervous System | | | |
| Depression | 20 (28) | 18 (38) | 38 (32) |
| Dizziness | 8 (11) | 5 (10) | 13 (11) |
| Hypertonia | 4 (6) | 0 (0) | 4 (3) |
| Insomnia | 30 (42) | 23 (48) | 53 (44) |
| Leg cramps | 7 (10) | 3 (6) | 10 (8) |
| Nervousness | 20 (28) | 20 (42) | 40 (33) |
| Paresthesia | 24 (33) | 15 (31) | 39 (33) |
| Vertigo | 12 (17) | 12 (25) | 24 (20) |

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| Respiratory System | | | |
| Cough increased | 4 (6) | 1 (2) | 5 (4) |
| Pharyngitis | 6 (8) | 4 (8) | 10 (8) |
| Rhinitis | 6 (8) | 7 (15) | 13 (11) |
| Urogenital System | | | |
| Breast pain | 21 (29) | 7 (15) | 28 (23) |
| Dysmenorrhea | 4 (6) | 3 (6) | 7 (6) |
| Metrorrhagia | 10 (14) | 3 (6) | 13 (11) |

Estrogens may increase plasma triglyceride levels, leading to pancreatitis in women with familial defects of lipoprotein metabolism.[3]

Substantial elevations in blood pressure have been reported in women taking estrogens, but such increases were not noted in clinical trials evaluating this product.[3]

There is an increased risk of venous thromboembolism (VTE) in women taking estrogens. The risk of VTE increases from about one case per 10,000 women per year in women not taking estrogens to about 2 to 3 cases per 10,000 in estrogen users. In addition, there is a 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women taking estrogens.[3]

Estrogens increase the risk of endometrial cancer, therefore, close monitoring, including appropriate diagnostic measures for persistent or recurring abnormal vaginal bleeding, is important. There are conflicting data on the relationship between estrogens and an increased risk of breast cancer.[3]

*Pregnancy and Lactation*

Estrogens are not indicated for use during pregnancy or the immediate postpartum period. Estrogen administration to nursing mothers decreases the quantity and quality of the milk.[3]

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**Drug Interactions**

There are numerous drug-laboratory test interactions in women taking estrogens, including tests for clotting time, thyroid, other binding proteins, cholesterol, glucose, and serum folate.[3]

The product information reports that there are no known drug interactions with estrogens.[3] However, numerous estrogen drug interactions are reported in the literature (Table 4). The clinical significance of these potential interactions in women treated with conjugated estrogens, A is unknown.

Table 4. Estrogen drug interactions[8]

| Precipitant Drug | Object Drug[a] | | Description |
|---|---|---|---|
| Estrogens | Anticoagulants, oral | ↓ | Estrogens may theoretically reduce the hypothrombinemic effect of anticoagulants |
| Estrogens | Antidepressants, tricyclic | ↔ | Pharmacologic effects of these agents may be altered by estrogens; the effects of this interaction may depend on the dose of the estrogen. An increased incidence of toxic reactions may also occur. |
| Barbiturates, rifampin | Estrogens | ↓ | Barbiturates, rifampin, and other agents that induce hepatic microsomal enzymes with concomitant estrogens may produce lower estrogen levels than expected. |
| Estrogens | Corticosteroids | ↑ | Estrogen coadministration may reduce the clearance and increase the elimination half-life of corticosteroids |
| Estrogens | Dantrolene | ↔ | While a definite drug interaction with dantrolene has not yet been established, observe caution with concomitant use. Hepatotoxicity has occurred more often in women >35 years of age receiving dantrolene and estrogen. |
| Hydantoins | Estrogens | ↓ | Breakthrough bleeding, spotting, and pregnancy have resulted when these medications were used concurrently. A loss of seizure control has also been suggested and may be due to fluid retention. |
| Estrogens | Hydantoins | | |

a. ↓ = object drug decreased; ↑ = object drug increased; ↔ = undetermined effect

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**Dosing**

The lowest dosage that will control symptoms should be used. The initial recommended dose is 0.625 mg daily with titration up to 1.25 mg daily. Treatment should be discontinued as promptly as possible, with attempts to discontinue or taper medication made at 3-month to 6-month intervals.[3]

Consideration should be given to adding progestin therapy in women who have not had a hysterectomy to reduce the incidence of endometrial hyperplasia.[3] A phase III study combining Cenestin™ with the progestin medroxyprogesterone is planned.[4]

Contraindications to the use of estrogens include known or suspected cancer of the breast, known or suspected estrogen-dependent neoplasia, known or suspected pregnancy, undiagnosed abnormal genital bleeding, active thrombophlebitis, thrombosis, or thromboembolic disorders, or a past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use.[3]

Synthetic conjugated estrogens should not be administered to pediatric patients.[3]

**Availability**

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Conjugated estrogens, A, available as Cenestin™ from Duramed Pharmaceuticals, Inc., was approved by the FDA on March 24, 1999. In addition to the active ingredient, tablets contain ethylcellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, polyethylene glycol, polysorbate 80, pregelatinized starch, titanium dioxide, and triethyl citrate. FD&C red no. 40 aluminum lake is also present in the 0.625 mg tablet.[3] The film-coated tablet is formulated to slowly release its contents over several hours.[11]

Cenestin™ was originally formulated to mimic the release properties of Premarin® (to be submitted as an ANDA). The Premarin® formulation is not dose proportional; the concentration/time profile of estrogens obtained from two 0.625 mg tablets is not equivalent to that obtained from one 1.25 mg tablet. After the decision not to approve this product as a generic

 

the FDA notified Duramed that they would prefer that this product's tablet strengths be dose proportional. In order to accomplish this, Duramed has re-formulated the 1.25 mg tablet and has now submitted that information to the FDA where approval is pending. Meanwhile, the 0.625-mg and 0.9-mg tablets were approved.

**Conclusions**

Synthetic conjugated estrogens are indicated for the short-term management of vasomotor symptoms of the menopause. The safety and efficacy of synthetic conjugated estrogens, A were established in one small short-term clinical trial published in abstract form. By 12 weeks, the estrogen reduced mean moderate-to-severe vasomotor symptoms by 81% vs baseline compared with a 58% reduction with placebo ($p < 0.010$). Adverse effects are similar to those seen with other estrogens. The usual dose is 1.25 mg daily.

**References**


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